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Dockets Management Branch
HFA 305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0524: Comments on FDA Draft Guidance for Industry ANDAs: Pharmaceutical Solid Polymorphism (Dec. 2004)

Dear Sir or Madam:

Eon Labs, Inc. respectfully submits this comment in response to the Draft Guidance on ANDA Polymorphism.

Comments;

1. The CMC requirements for new drugs (NDAs) and for generic drugs (ANDAs) should be the same. Therefore, the Guidance should NOT be specific for ANDAs. The NDA applicant (or its active pharmaceutical ingredient ("API") supplier) is in the same position to characterize its polymorphic form as is any ANDA applicant.

2. Characterization of the polymorph of the API should be the responsibility of the API manufacturer, NOT the finished dosage form (generic) manufacturer. It is, however, reasonable that the generic drug product manufacturer sets quality standards (specifications) for all raw materials, including the API, that are included in the manufacture of the finished dosage product. Often, a formulator filing an ANDA will reference the DMF of the API supplier, the API supplier is in the best position to characterize its polymorph. To the extent that the polymorph information must be submitted to the FDA – which is not entirely clear at the

moment (see point #9 below) – this information could be included as part of the DMF. The sponsor of the ANDA is not necessarily the API supplier.

3. The generic manufacturer is responsible for demonstrating that the proposed generic drug product is a therapeutic equivalent to the reference-listed drug (RLD) as defined in the Orange Book. To this end, the proposed generic drug product is *de facto* compared to the RLD. To make such a comparison, therefore, there must be something against which to compare. Unless and until the NDA applicant submits any polymorphic information to the FDA and the FDA publishes that information as part of the Summary Basis of Approval (SBOA), the ANDA applicant cannot compare its polymorphic data to the RLD polymorphic data. Thus, no comparison can be made and requiring any ANDA applicant or API supplier to characterize the polymorph is of no benefit to the Agency and represents an undue/needless expense on the API supplier or the ANDA applicant. That is, requiring polymorphic information when it is unknown if the agency will need it for comparison purposes against the RLD is simply a needless exercise. The Agency should decide first whether an NDA applicant is required to submit polymorphic information to the Agency and publish it before requiring an ANDA applicant to do so (see also point #8 below).

4. During the manufacture of a finished dosage form, the polymorphic form of the initial API may change into another polymorph or into a mixture of polymorphs. The characterization of the polymorphic form of the API after incorporation into the finished drug product is difficult. The Draft Guidance is unclear on whether the polymorphic information is required for the bulk API, the finished dosage form, and the details if the finished dosage form polymorphic data is indeed unobtainable.

5. We agree with the Agency that different polymorphs of the same API MAY have different physico-chemical characteristics such as the rate of dissolution, stability, etc. APIs that exist in different polymorphs can be handled similar to the regime governing APIs that exist in different solvates (e.g., hydrous, hemihydrous, and anhydrous). It is well known that different solvates also have different physico-chemical activities. It is, however, the responsibility of the generic manufacturer to demonstrate that the generic drug product meets all the requirements for therapeutic equivalence including, but not limited to:

a. Bioequivalent *in vivo* when compared to the RLD
b. Stable over the expected shelf life of the product

It should be noted that drug products with different rates of drug dissolution may still be bioequivalent, *in vivo* and that the excipients in the formulation may improve the stability and dissolution of the API.

6. Setting a specification the polymorphs in solid oral and suspension dosage form products:

The decision trees provided in this Draft Guidance and the setting of specifications for the API polymorph by the generic manufacturer overburden the industry and force the industry to provide information that will not improve the quality and safety of the manufactured drug product. The present CMC requirements for BOTH NDAs and ANDAs are sufficient for drug product manufacturer to assure quality.

7. The concept of "sameness" should be considered equally by the Agency for different polymorphs as presently considered for anhydrous and hydrous forms of the API. Under this doctrine, all polymorphic forms of the API should be considered "same" in terms of a pharmaceutical equivalent. It is the responsibility of the generic drug product manufacturer to also show that the drug product is bioequivalent and meets the CMC and labeling requirements presently in place for ANDA review and approval.

8. The Draft Guidance has indicated that the Agency has considered and approved polymorphs. The Draft Guidance, however, does not explicate that the difference in polymorphs have had any effect on safety or efficacy. To this end, the Draft Guidance simply iterates that the polymorphs may be different and ought to be characterized. Because the FDA has not yet published any reports that *bona fide* question the safety and efficacy of polymorphs (as opposed to simply reciting truisms that polymorphs can have different chemical characteristics), to require ANDA applicants to characterize the polymorph represents a needless expense and undue burden.

9. The Draft Guidance does not explain what the polymorph information will be used for by the Agency. For example, on the data is obtained, it is unclear whether the Agency will require that information be submitted as part of the ANDA or whether that information will remain in the ANDA applicant facility (like laboratory notebooks) for the Agency to request, if necessary. Eon further notes that under 21 C.F.R. §314.53(b)(1), the NDA applicant is required to ascertain its polymorph information *vis a vis* any listed patent and that under (b)(2), is required to submit the information. Eon will take great issue with the FDA if the FDA requires such information to be submitted as part of the ANDA without requiring the NDA applicant to publish or make its polymorph data equivalently accessible. This will avoid the awkward situation where an NDA holder lists a polymorphic patent in the Orange Book, the ANDA applicant includes a Para. IV certification to the polymorphic patent, the NDA holder then sues and propounds discovery to obtain the ANDA polymorphic data, but the ANDA applicant is not able to obtain the NDA polymorphic data. In this situation, the NDA holder can discover ANDA data but the NDA holder can hide its own polymorphic data. To this end,

polymorphic data for listed patents should be published in the SBOA or if not published, then fully accessible in unredacted form *vis a vis* a FOIA request.

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Eon appreciates the opportunity to respond to the Draft Guidance and remains available to follow up with additional comments should the Agency so desire.

Sincerely,

/s/ Shashank Upadhye, Esq.
Vice President and Counsel

Cc: Mr. Gary Buehler, Office of Generic Drugs, FDA